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(81) Designated States (unless otherwise indicated, for every
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GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
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Declarations under Rule 4.17:

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EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
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KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT,
LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
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JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM,
ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD,
SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT,
LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
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— as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii)) for all designations

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for the following desig-
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW,
BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ,
EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID,
IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ,
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA,
ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ,
SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,

[Continued on next page]

(54) Title: **HUMAN IL-1 BETA ANTAGONISTS**

(57) Abstract: The present invention encompasses isolated antibodies, or antigen-binding portions thereof, that specifically bind mature human IL-1 Beta. These antibodies, or antigen-binding portions thereof, generally exhibit high binding affinities (low $K_{0.5}$ values), reduced deamidation compared to the native antibody, and can be used to treat various diseases such as rheumatoid arthritis, osteoarthritis, or neuroinflammation.

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INTERNATIONAL SEARCH REPORT

national Application No
R/US2004/000019

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K16/24 C12N15/13 C12N15/85 C12N5/10 A61K39/395
A61P19/02 A61P37/00 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 95/01997 A (GROSS MITCHELL STUART ; HURLE MARK ROBERT (US); JACKSON JEFFREY RICHA) 19 January 1995 (1995-01-19) page 3, line 5 - line 19 page 21, line 28 - line 19 claims; examples | 1-35 |
| Y | WO 01/64751 A (MEDIMMUNE INC) 7 September 2001 (2001-09-07) page 2, line 9 - page 3, line 3 page 15, line 12 - line 21 page 16, line 30 - page 17, line 26 page 18, line 11 - page 19, line 12 claims; examples ----- -/-- | 1-35 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA

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Rankin, R

INTERNATIONAL SEARCH REPORT

mational Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | JACKSON J R ET AL: "IN VITRO ANTIBODY MUTARATION IMPROVEMENT OF A HIGH AFFINITY, NEUTRALIZING ANTIBODY AGAINST IL-1BETA" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 154, no. 7, 1 April 1995 (1995-04-01), pages 3310-3319, XP000941315 ISSN: 0022-1767 the whole document | 1-35 |
| P,X | WO 03/010282 A (JIA AUDREY YUNHUA ; KUHSTOSS STUART ALLEN (US); VASQUEZ MAXIMILIANO J) 6 February 2003 (2003-02-06) page 2, line 6 - page 3, line 14 page 8, line 18 - page 10, line 25 page 11, line 14 - page 12, line 15 page 23, line 14 - page 24, line 2 page 24, line 26 - page 26, line 16 claims; examples | 1,2,24, 26,29-35 |
| P,X | WO 03/073982 A (ROGERS DANISE PAIGE ; HUANG LIHUA (US); LU JIRONG (US); LILLY CO ELI () 12 September 2003 (2003-09-12) page 1, line 20 - page 2, line 2 page 9, line 4 - line 36 claims; examples | 1,2,24, 26,29-35 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2004/000019

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing
 - ☒ contained in the international application as filed
 - ☒ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purpose of search
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 30, 31 and 34 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

:T/US2004/000019

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9501997 | A | 19-01-1995 | WO 9501997 A1 | 19-01-1995 |
| WO 0164751 | A | 07-09-2001 | AU 4002001 A | 12-09-2001 |
| | | | CA 2401652 A1 | 07-09-2001 |
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| | | | JP 2003525061 T | 26-08-2003 |
| | | | WO 0164751 A2 | 07-09-2001 |
| | | | US 2002098189 A1 | 25-07-2002 |
| WO 03010282 | A | 06-02-2003 | EP 1423432 A2 | 02-06-2004 |
| | | | WO 03010282 A2 | 06-02-2003 |
| WO 03073982 | A | 12-09-2003 | WO 03073982 A2 | 12-09-2003 |



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